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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/485,298	02/08/00	YAMAMOTO J	1422-411P

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EXAMINER	
CHAKRABARTI,A	

ART UNIT	PAPER NUMBER
1655	13

DATE MAILED: 05/24/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/485,298	Yamamoto et al.
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Apr 24, 2001 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 20-37 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 20-37 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1. A request for continued examination under 37 CAR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CAR 1.114, and the fee set forth in 37 CAR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CAR 1.114. Applicant's submission filed on February 26, 2001 has been entered.

Specification

2. Claims 17-19 have been canceled without prejudice towards further prosecution.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 20-25 and 27-29 are rejected under 35 U.S.C 103 (a) over Dower et al. (U.S. Patent 5,639,603) (June 17, 1997) in view of Koster et al. (U.S.Patent 6,043,031) (March 28, 2000).

Dower et al teach a method for amplifying a DNA by polymerase chain reaction by the use of a DNA fragment comprising a nucleotide analog as a template (Column 27, lines 3-30).

Dower et al teach a method for amplifying a DNA characterized in that the DNA fragment is a cDNA prepared by reverse transcription reaction using an RNA as a template (Column 35, lines 40-64).

Dower et al do not teach the method for amplifying a DNA in the presence of two or more kinds of nucleotide analogs.

Koster et al teach the method for amplifying a DNA in the presence of two or more kinds of nucleotide analogs (7-Deaza-dGTP) to be incorporated in a DNA strand in place of dGTP and at least one nucleotide analog is incorporated in the amplifying step in place of dATP (Example 8, Column 30, line 64 to column 33, line 27 and Table 1). In addition, Koster et al teach a template containing nucleotide analog formed during PCR (Column 33, lines 12-16).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the modified nucleotide analogues model of Koster et al with the methods of amplifying nucleic acids using modified nucleotide template of Dower et al ., since Koster et al state, "The process of the invention provide for increased accuracy and reliability of nucleic acid detection. In addition, the process allows for rigorous controls to prevent false negative or positive results. The processes of the invention avoid electrophoretic steps; labeling and subsequent detection of a label. In fact it is estimated that the entire procedure, including nucleic acid isolation, amplification, and mass spec analysis requires only about 2-3 hours time. Therefore, the instant disclosed processes of the invention are faster and less expensive to perform than existing DNA detection systems. In addition, because the instant disclosed processes allow the nucleic acid fragments to be identified and detected at the same time by their specific molecular weights (an unambiguous physical standard), the disclosed processes are also much more accurate and reliable than currently available procedures (Column 5, lines 26-42)". An ordinary artisan would have been motivated by these express statements of Koster et al to combine the modified nucleotide analogues model of Koster et al with the methods of amplifying nucleic acids using modified nucleotide template of Dower et al., in order to achieve the express advantages of modified nucleotide analogues, as noted by Koster et al , which provides for increased accuracy and reliability of nucleic acid detection and in addition allows for rigorous controls to prevent false negative or positive results which avoids electrophoretic steps; labeling and subsequent detection of a label and which are faster and less

expensive to perform than existing DNA detection systems and in addition which allows the nucleic acid fragments to be identified and detected at the same time by their specific molecular weights (an unambiguous physical standard) thereby rendering the process also much more accurate and reliable than currently available procedures.

5. Claims 20-30 are rejected under 35 U.S.C 103 (a) over Dower et al. (U.S. Patent 5,639,603) (June 17, 1997) in view of Koster et al. (U.S.Patent 6,043,031) (March 28, 2000) further in view of Dodge et al. (U.S. Patent 5,912,117) (June 15, 1999).

Dower et al in view of Koster et al teach the method of claims 20-25 and 27-29 as described above.

Dower et al in view of Koster et al do not teach the compounds for lowering the *Tm* value of a double-stranded nucleic acid.

Dodge et al teach the compounds (glycerol and DMSO) for lowering the *Tm* value of a double-stranded nucleic acid.(Column 8, line 49 to column 9, line 4).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the compounds for lowering Tm of duplex DNA of Dodge et al with the fast and accurate methods of amplifying nucleic acids using modified nucleotide template and nucleotides of Dower et al in view of Koster et al., since Dodge et al state, "To assure PCR efficiency, glycerol and other related solvents such as dimethyl sulfoxide, can be used to increase the sensitivity of the PCR at the amplification level and to overcome problems pertaining to the sequencing of regions of DNA having strong secondary

structure. These problems may include : (1) low efficiency of the PCR, due to a high frequency of templates that are not fully extended by the polymerizing agent or (2) incomplete denaturation of the duplex DNA at high temperatures, due to high GC content. The use of such solvents increases the sensitivity of the assay at the level of amplification to approximately several femtograms of DNA (which is believed to correspond to a single spirochete cell). This level of sensitivity eliminates the need to detect amplified target DNA using a probe, and thereby dispenses with the requirements for radioactive probes, gel electrophoresis, Southern blotting, filter hybridization, washing and autoradiography (Column 8, line 49 to column 9, line 2)". An ordinary artisan would have been motivated by these express statements of Dodge et al to substitute and combine the compounds for lowering Tm of duplex DNA of Dodge et al with the fast and accurate methods of amplifying nucleic acids using modified nucleotide template and nucleotides of Dower et al in view of Koster et al., in order to achieve the express advantages of solvents, as noted by Dodge et al , which provides assurance of PCR efficiency and increases the sensitivity of the PCR at the amplification level to overcome problems pertaining to the sequencing of regions of DNA having strong secondary structure including : (1) low efficiency of the PCR, due to a high frequency of templates that are not fully extended by the polymerizing agent or (2) incomplete denaturation of the duplex DNA at high temperatures, due to high GC content and in addition, increases the sensitivity of the assay at the level of amplification to approximately several femtograms of DNA (which is believed to correspond to a single spirochete cell) which eliminates the need to detect amplified target DNA using a probe, and

thereby dispenses with the requirements for radioactive probes, gel electrophoresis, Southern blotting, filter hybridization, washing and autoradiography.

6. Claims 20-37 are rejected under 35 U.S.C 103 (a) over Dower et al. (U.S. Patent 5,639,603) (June 17, 1997) in view of Koster et al. (U.S.Patent 6,043,031) (March 28, 2000) further in view of Dodge et al. (U.S. Patent 5,912,117) (June 15, 1999) further in view of Stratagene Catalog (1988, Page 39).

Dower et al. in view of Koster et al. further in view of Dodge et al. expressly teach the method claims of 20-30 including all the modified nucleotide templates, analogues and compounds for lowering the *Tm* value of a double-stranded nucleic acid as described above in detail.

Dower et al. in view of Koster et al. further in view of Dodge et al do not teach the motivation to combine all the reagents for amplifying a nucleic acid in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine a suitable container and all the modified nucleotide templates, analogues and compounds for lowering the *Tm* value of a double-stranded nucleic acid as taught by Dower et al. in view of Koster et al. further in view of Dodge et al, into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and pre-mixed specifically for a defined set of

experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control". (page 39, column 1).

Response to Arguments

7. Applicant's arguments filed on February 26, 2001, have been fully considered but they are not persuasive.

Applicant argues that Dower and Koster references cannot be combined. This argument is not persuasive, especially in the presence of a strong motivation provided by Koster, "The process of the invention provide for increased accuracy and reliability of nucleic acid detection. In addition, the process allows for rigorous controls to prevent false negative or positive results. The process of the invention provides electrophoretic steps; labeling and subsequent detection of a label. In fact it is estimated that the entire procedure, including nucleic acid isolation, amplification and mass spec analysis requires only about 2-3 hours time. Therefore, the instant disclosed processes of the invention are faster and less expensive to perform than existing DNA

detection systems. In addition, because the instant disclosed processes allow the nucleic acid fragments to be identified and detected at the same time by their specific molecular weights (an unambiguous physical standard), the disclosed processes are also much more accurate and reliable than currently available procedures (Column 5, lines 26-42)".

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For example, it was mentioned clearly in the last office action that Dower reference does not teach two or more kinds of nucleotide analogs, only Koster reference teaches the same. Similarly, uniform incorporation of analog is taught by Dower, not Koster.

In response to applicant's argument that cited references used their method for another purpose, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., nucleotide analogs are incorporated into the synthesized chain at a uniform frequency without being affected by the GC content of template) are not recited in the rejected claim(s). Although the claims are

interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to the applicant's argument that Dower reference teaches an extra step of acid treatment, it is noted that the "comprising" language of the instant claims permits any additional steps to be included with the claimed invention.

Applicant also argues that neither references teaches amplification of nucleic acid template containing nucleic acid analogs in the presence of nucleotide analog. This argument is not persuasive. Dower reference clearly teaches amplification of nucleic acid template containing nucleic acid analogs in the presence of nucleotide analog (Column 33, lines 12-16).

In view of this response to arguments, all rejections made in the last office action are hereby being maintained.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

Arun Chakrabarti,

Patent Examiner,

May 9, 2001